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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,008	TAKAMI ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9 and 11* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group 2 claims 5-11, and the combination of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21 in the reply filed on 6/13/2008 is acknowledged.

Claims 1-4 has withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/13/2008.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-11 are pending and being examined.

Claim Objections

2. Claim 10 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Claim 10 is a method of claim 5 comprising a variation rate of gene expression with a standard value obtained from claims 7 or 9. Claim 10 thus requires the limitations of claim 5 and claim 7 or claim 9 and thus is improper. See MPEP § 608.01(n). Accordingly, the claim 10 not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5-9 and 11are rejected under 35 U.S.C. 112, first paragraph, because the specification and art , while being enabling for a method of detecting variation of expression of genes by phospholipidosis inducing compounds in a mammalian cell comprising: treating a mammalian cell with a compound known to cause phospholipidosis, detecting expression of genes showing variation in gene expression by phospholipidosis inducing compounds in said mammalian cell, does not reasonably provide enablement for the breadth of the methods claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and the breadth of the claims:</u>

Claim 5 is drawn to a method of predicting phospholipidosis induction potential in a compound comprising detecting expression variation of one or more genes showing expression variation in correlation with phospholipidosis in a sample containing a mammalian cell exposed to the compound or a sample taken from a mammal administered with the compound.

Claim 5 thus broadly encompasses the predicting phospholipidosis potential of "any" compound in "any" sample of "any" tissue by altered gene expression of "any" gene.

Claim 6 further draws the claims to the elected combination of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Claim 7 is drawn to a method of determining a standard for judgment of the possible phospholipidosis by a compound comprising: detecting the variation in one or more gene in samples containing mammalian cells exposed to two or more phospholipidosis inducing compounds and two or more known phospholipidosis non-inducing compounds or samples taken from mammals administer with each of said compounds and using a standard value average variation rate capable of correctly judging the presence or absence of phospholipidosis induction potential of the compounds by not less than about 70% based on average expression variation.

Thus claim 7 as presented requires samples containing a mammalian cell exposed to each of two or more phospholipidosis inducing compounds and two non-phospholipidosis inducing compounds. Thus the claim requires treatment of mammalian cells with at least 4 compounds and then detection of gene expression.

Claim 8 further draws the claims to the elected combination of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Claim 9 is drawn to a method of validating the standard for other compounds known for induction of phospholipidosis and known not to induce phospholipidosis.

Claim 11 is drawn to predicting the toxicity of a compound comprising detecting expression variation in correlation with toxicity expression in a sample contain a mammalian cell exposed to a compound or a sample taken from a mammal administer the compound and judging the presence or absence of toxicity of the compound.

Claim 11 thus broadly encompasses determining the toxicity of "any" compound in "any" tissue in "any" mammal by analysis of a cell treated with a compound or administration of the compound to a mammal and expression analysis of "any" tissue.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches the instant invention relates to methods of predicting toxicity of drugs (1st paragraph, page 1).

The specification teaches the cell can be any cell from a mammal (page 24, lines 23-25). The specification further teaches that a mammal includes human and non-human mammals (page 25, lines 25-29).

the "average variation rate" is defined as follows. That is, an expression amount is measured for each marker gene when mammal (cells) is and is not exposed to a test compound and when the expression amount increased upon exposure, its magnification (e.g., 2 when increased two-fold) is taken as an expression variation rate (X) of each gene, and when the expression amount decreased, an inverse number of its magnification (e.g., 2 when decreased to 1/2) is taken as an expression variation rate

(X) of each gene, and an average value of the expression variation rate of the total marker genes (n genes) is defined to be an average variation rate (following formula).

Average variation rate = $m_1X_1+m_2X_2+\ldots+m_nX_n$

(m1+m2+---+mn=l)

wherein mi(i=l-n) shows the weight of each gene. While the weight is not particularly limited, it is preferably mi×n=0.2-5, for example, it is the same weight for all (mi=i/n). (page 29)

The specification teaches screening of hepatoxicity be done on hepatocytes (page 35, lines 33-top page 36).

The specification teaches, "Moreover, by accumulating the data relating to known compounds by evaluation by the present method and microscopic observation, extremely accurate prediction of compound groups unknown as to the presence or absence of a PLsis induction potential becomes possible" (page 35, lines 23-27). Thus the specification suggests the gene analysis method requires an additional step of microscopic for extremely accurate prediction of PLsis.

The specification in example 1 teaches electromicroscopic analysis of 30 compounds on HepG2 cells (pages 37-40).

The specification teaches in example 2 gene expression variation of PLsis inducing genes in HEPG2 cells. The specification teaches HEPG2 cells were exposed to 17 PLsis inducing compounds and 14 PLsis non-inducing compounds for 24 hours (page 41, lines 5-10). The specification teaches the cells were frozen and RNA was analyzed. The specification teaches primers and probes were designed based on the sequences of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21. It is noted the

specification provides no data or suggestion on how these nucleic acid sequences were chosen as markers.

The specification teaches, "For each test compound, the expression variation rate of 12 genes each relative to the control group was determined. The results are shown in Table 2. In all the 12 genes examined, there was a tendency toward variation in their expression due to the exposure to a PLsis-inducing compound, and substantially no variation in their expression due to the exposure to a PLsis non-inducing compound. Therefore, it has been clarified that these 12 genes are marker genes useful for the prediction of a PLsis induction potential of a drug." Thus the specification teaches exposure of cells to "each test compound" resulted in an expression variation in the cells studied. The specification teaches all known PLsis inducing compounds resulted in an average 1.5 variation rate and 12 of 13 non-PLsis inducing compounds resulted in a variation rate of less than 1.5 (page 46, lines 10-17). Example 2 teaches addition of single compounds to cells and analysis of the cells after single treatment, which does not demonstrate predictability of treating at a cell with multiple compounds at once or sequentially and examining gene variation as claimed in claims7-9.

The specification in example 3 confirms the findings of example 2 by use of 26 compounds for determination of presence or absence of PLsis induction potential.

The state of prior art and the predictability or unpredictability of the art:

Reasor et al (Experimental Biology and Medicine (2001) volume 226, pages 825-830) teaches, "The induction of phospholipidosis by CADs is a dose-dependent process, with its development being directly proportional to the accumulation of CAD in

the cell or tissue. The phospholipids in cells may be of intracellular or extracellular origin. The phospholipidosis is a generalized phenomenon in that the lamellar bodies may occur in virtually any tissue, with the lungs and liver being common targets. No species or age group appears to be excluded from their induction. Different species, strains within species, and age groups may respond dissimilarly, however, to the same CAD (20, 34–36). Within the same species, different CADs may exhibit different tissue specificity, qualitatively and quantitatively, for the induction of the condition. Consequently, the response of a given species to a particular CAD is both qualitatively and quantitatively unpredictable" (page 827, 1st column, 1st paragraph). Reasor continues, "Because of the variability among species, or a particular strain within a species, in the induction of phospholipidosis, caution must be exercised in predicting the susceptibility of humans based on results in animals. The role of rat strain and other confounding factors in the interpretation of toxicity data have been reviewed" (page 827, 1st column, 2nd paragraph). Reasor teaches that different phospholipidosis inducing compounds have different effects on different species, tissues, strains and ages. It would thus be unpredictable to predict toxicity or phospholipidosis induction ability of a compound in one species or tissue with toxicity of phospholipidosis induction potential without a specific nexus for such extrapolation.

Williams (Cancer Research (2000) volume 60, pages 6045-6051) teaches, "A crucial observation from these studies is that treatment with 10 mM or less of celecoxib for 3 days has no detectable effect on cell death *in vitro*. Despite this lack of effect in cultured cells, we found that celecoxib strongly attenuated the growth of xenografted

HCA-7 tumors *in vivo*, although the plasma concentration of celecoxib was 2.3 mM. This discrepancy highlights the fact that tumor growth *in vivo* is determined by the interaction between factors intrinsic to tumor cells, the extracellular matrix, stromal cells, and other host factors. These factors are not always present *in vitro* when cells are grown on plastic culture dishes. Cell culture models are often used to evaluate the therapeutic potential of NSAIDs against cancer, but great caution needs to be taken when extrapolating *in-vitro* results to the whole organism, particularly with respect to the relative dose of agent used" (page 6049, 2nd column, full paragraph). Williams thus teaches it is unpredictable to extrapolate the toxicity data of compounds in vitro to in vivo due to factors intrinsic to the cell as well as other host cell factors.

Vandesompele teaches, "Accurate normalization of gene expression levels is an absolute prerequisite for reliable results, especially when the biological significance of subtle gene expression differences is studied" (see page 9, 2nd column, discussion) (Vandesompele et al (Genome Biology (2002) volume 3, pages 1-11). Vandesompele teaches, "That the conventional use of single gene normalization leads to relatively large errors in a significant portion of samples tested" (see abstract, results). Vandesompele teaches that ACTB (beta actin) appears to be the one of the worst genes for normalization and thus resulting in large normalization errors (see page 10, 1st paragraph). Vandesompele teaches at least 3 housekeeping genes are required for accurate normalization (see page 10, 1st column, 1st full paragraph). Vandesompele thus teaches that studies of gene expression using a single gene for normalization are unpredictable due to the large variation in the expression of the genes used for

normalization.

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression

is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Van Pelt et al (Molecular and Cellular biochemistry (2003) volume 243, pages 49-54) teaches that there are variant strains of HepG2 cells (abstract). Van Pelt teaches, "The removal of lidocaine and its conversion to MEGX was assayed. Table 3 shows that the cell lines H7D7-A and H7D7- B removed lidocaine at a substantial higher rate (3-fold) than HepG2 cells; however, this was still only one-third of the rate observed with primary human hepatocytes. The production of MEGX by the different cell lines was 3% or less of that obtained with human hepatocytes" (page 53, 1st column, 2nd paragraph). From this data Van Pelt concludes, "Biochemical analysis of these HepG2 sub-clones revealed that some metabolic properties are quantitatively altered, which could render some more useful for toxicological or pharmacological studies" (page 53, 2nd column, 2nd full paragraph). Van Pelt thus teaches there is variability in drug metabolism and drug response between different subclones of HEPG2 cells. Thus due to the variability (unpredictability) of the different clones of HEPG2 cells it would be unpredictable to associate altered drug metabolism in one cell line with another cell line.

Post-filing art of Nioi et al (Toxilogical Sciences (2007) volume 99, pages 162-173) presents a study to validate a study of instant inventors and specification. Nioi et al reiterates that even after filing it is established that different drugs affect different cells differently , "It is important to note that both erythromycin and quinidine are known to cause PLD in vivo and in vitro in other cell types" (page 164, 1st column, last paragraph). Nioi teaches that 5 of the 8 drugs known to cause PLsis had predictability

index of greater than 1.5, which is the measure the instant specification uses. However, Nioi teaches that 3 of the 8 (but amiodarone, loratadine, and tamoxifen) all had scores < 1.5 (page 165, 1st column, 1st full paragraph). Nioi et al continues, "Our results are consistent with the previously published data with a couple of notable differences (Table 4). Sawada et al. (2005) identified amiodarone, loratadine, and tamoxifen as PLD-inducing drugs with PI scores of 1.61, 1.59, and 2.15, respectively, whereas in our study all of these compounds had PI scores < 1.5 (Table 4). Consistent with our data, Atienzar et al. (2006) also generated PI scores of < 1.5 for amiodarone and tamoxifen; they did not examine loratadine (Table 4). The only other major difference in the three data sets was with fluoxetine which had a PI score consistent with it inducing PLD in our study (1.99) and in Sawada's study (3.29) but not in Atienzar's experiment (1.27) (Table 4)" (page 165, bottom 1st column to top of 2nd column). Nioi teaches that increasing doses of PLsis inducing compounds led to increase PI and thus correct prediction. Nioi teaches, "We found that only five of eight of the positive control compounds were correctly identified when a single concentration of drug was used, and these findings were consistent between experiments" (page 170). Nioi suggests that while gene expression analysis is useful, the use of multiple drug concentration improves the accuracy (predictability) of the method (page 172, 1st column, last paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between phospholipidosis or toxicity of "any" compound and gene expression in "any" mammalian cell exposed to the compound or from a sample taken from a mammal administered with the compound. The artisan would have to undertake undue and unpredictable trial and error experimentation to predictably determine which compounds are phospholipidosis inducing or toxic as Reasor teaches that PLsis and thus toxic effects are dose, age, species and tissue dependent. It would thus be unpredictable to use a single assay at a single does of a compound to determine the toxicity of a compound, as there is known variability as taught by Reasor.

Further it would be unpredictable to make a determination of toxicity or phospholipidosis of a compound as Williams teaches that the in vivo effects of a drug cannot be predictably extrapolated to in vitro effects or vice due to intrinsic factor of the cell and host factors, without specific guidance.

Further it would be unpredictable to correlate gene expression with any phenotype in this case drug toxicity or phospholipidosis without specific guidance on normalization of the gene expression data in the cells as Vandesompele teaches that the use of a single gene for normalization results in great variability. Further it would be unpredictable as Cheung teaches there is a large natural variation in individuals. Due to Cheung's teachings the artisan would have to undertake trial and error experimentation to determine if treatment of the drug is due to drug response or normal genetic variation in subjects or cell culture due to the teachings of Van Pelt. The teachings of Newton

and Wu continue to demonstrate the importance of normalization and unpredictability associated with improper or poor normalization.

Further it would be unpredictable to extrapolate the teachings of one cell line for another due to the variations in cell lines taught by Van Pelt. Specifically Van Pelt teaches that different subclones of HEPG2 cells have different drug metabolism rates. It would thus be unpredictable to extrapolate differences observed in one clone of a cell line with a different clone without specific confirmation or guidance, due to the variability taught by Van Pelt.

Further it would be unpredictable to practice the invention as claimed as post-filing art of Nioi teaches the inability to predictably confirm the phospholipidosis inducing ability of compounds known phospholipidosis inducing compounds. Nioi teaches that 3 known phospholipidosis inducing compounds were identified as non-inducing phospholipidosis compounds using the instant method. Nioi teaches that use of increasing doses did improve the predictability of the method. Nioi further demonstrated there was significant variability between assays that would result in differential classification of compounds.

Further the specification provides no guidance on how to determine a standard of judgment based on the treatment of a single cell sample with two inducing compounds and two non-inducing compounds as required by claims 7-9. It would thus be unpredictable to determine the phospholipidosis induction potential of a single compound when the claim requires the use of at least 3 other compounds one of which is known to have a similar effect. It would be further unpredictable as one of more of

the compounds treated could have an opposing effect on the genes of interest and thus result in a lack of variation, by canceling out the effect. It is noted that screening of compounds in libraries by treatment of cells to identify possible leads compound was known at the time of the invention, however it would have been unpredictable to use a combination of 2 inducing compounds and 2 non-inducing compounds to predictably determine a standard for judgment without specific guidance as to the treatment of a cell with the four compounds. As the inducing and/or non-inducing compounds together may drug interaction affects and the instant specification provides no guidance how to predictably determine the effect of a single compound on a cell that has been treated with 4 compounds.

While the specification and art are enabling for a method of detecting variation of expression of genes by phospholipidosis inducing compounds in a mammalian cell comprising: treating a mammalian cell with a compound known to cause phospholipidosis, detecting expression of genes showing variation in gene expression by phospholipidosis inducing compounds in said mammalian cell, does not reasonably provide enablement for the breadth of the methods claimed

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation to predictably use the invention as claimed.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable

experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 7 is drawn to a method for determining the standard of judgment of the presence or absence of a phospholipidosis induction potential for a compound. However, step (1) of claim requires the treatment of samples containing mammalian cells to be exposed to two or more phospholipidosis inducing compounds and two or more phospholipidosis non-inducing. It is unclear how the artisan would determine the presence or absence of a phospholipidosis potential for a compound by treatment of a cell with at least four compounds. Claims 8 and 9 depend from claim 7 and thus have all the limitations of claim 7.

Further claim 9 further comprises similar analysis of other phospholipidosis inducing and non-inducing compounds. Thus it is unclear if claim 9 is intended to require the use of compounds in addition to those previously required of claim 7 or in substitution for those of claim 7. Further it is unclear how the artisan would determine the validity of the standard value for a compound when the claims require at least 2 inducers and two non-inducers.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Waring et al (Environmental Health Perspective (2003) volume 111, pages 863-870, available online 18, November 2002).

As noted in the MPEP 2111.02, “If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention’s limitations, then the preamble is not considered a limitation and is of no significance to claim construction.” Accordingly, the claim language of "a method for of predicting phospholipidosis induction potential of a compound” merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

This rejection is consistent with the scope of enablement as it is directed to active steps of the claimed invention.

Claim 5 is drawn to a method of detecting expression variation in one or more genes in correlation with phospholipidosis expression in a sample from mammalian cell exposed to a compound.

With regards to claim 5, Waring teachings treating rat liver cells with 52 different compounds including those that induce phospholipidosis (page 865, 1st column, 2nd full

paragraph). Waring teaches a subtractive hybridization was done to identify gene that were up regulated and down regulated (page 865, 1st column, last paragraph).

9. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Mendrick et al (WO02/095000, published November 28, 2002).

With regards to claim 11, Mendrick teaches a method of determining markers of the toxicity of a compound by gene expression. Mendrick teaches nucleic acid samples are isolated from cells that have been exposed to compounds, drugs, composition (page 36 line 30- top of page 37). Mendrick teaches Mendrick teaches, "Linear discriminant analysis uses both the individual measurements of each gene and the calculated measurements of all combinations of genes to classify samples. For each gene a weight is derived from the mean and standard deviation of the toxic and nontox groups. Every gene is multiplied by a weight and the sum of these values results in a collective discriminate score. This discriminant score is then compared against collective centroids of the tox and nontox groups. These centroids are the average of all tox and nontox samples respectively. Therefore, each gene contributes to the overall prediction. This contribution is dependent on weights that are large positive or negative numbers if the relative distances between the tox and nontox samples for that gene are large and small numbers if the relative distances are small. The discriminant score for each unknown sample and centroid values can be used to calculate a probability between zero and one as to the group in which the unknown sample belongs" (page 49, last paragraph). Mendrick thus teaches a method of predicting toxicity of a compound by exposing a sample form a mammalian cells to a compound, determining gene

expression and judging based on the average variation rate the presence or absence of toxicity.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Waring et al (Environmental Health Perspective (2003) volume 111, pages 863-870, available online 18, November 2002) of Wells et al (Physiological genomics (2003) volume 14 pages 149-159).

As noted in the MPEP 2111.02, “If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition

of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." Accordingly, the claim language of "a method for of predicting phospholipidosis induction potential of a compound" merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

This rejection is consistent with the scope of enablement as it is directed to active steps of the claimed invention.

Claim 5 and 6 are drawn to the detection of variation of one or more of the genes, but does not limit the method of detecting the gene the gene to those which are varied. Thus the claims broadly encompass detection of a portion of the gene and the specification nucleic acids are probes of 15 nucleotides or more.

Waring teaches treating rat liver cells with 52 different compounds including those that induce phospholipidosis (page 865, 1st column, 2nd full paragraph). Waring teaches a subtractive hybridization was done to identify gene that were up regulated and down regulated (page 865, 1st column, last paragraph).

Waring does not teach the detection of genes of the sequence or substantially same sequence of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Wells teaches the use of the Affymetrix U133A and U133B chip, which comprises 44,000 probes to 33,000 human mRNA including those of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the U133A array of Affymetrix for

the detection method of Waring. The artisan would be motivated to substitute the array of Wells in the method of Waring as the U133A and U133B array of Wells would allow for the detection of more transcripts and detection of human transcripts. Substitution of arrays of Wells for the method of Waring would allow the artisan to determine gene expression and thus toxic or phospholipidosis response in human cells without the need of manufacturing new microarrays and would allow for detection of expression of SEQ ID NO 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Summary

NO claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Examiner, Art Unit 1634

Steven Pohnert